

REMARKS

Claims 1-3 and 5-12 are pending in the present application. By virtue of this response, claim 1 has been amended and new claim 70 has been added. Accordingly, claims 1-3, 5-12 and 70 are currently under consideration. Claim 1 has been amended solely for purposes of clarification and without acquiescing to the rejection. Support for the claim amendment can be found throughout the specification; for example, page 34, lines 5-19. Support for new claim 70 can be found at least on page 34, lines 5-19; page 38 lines 3- 27; Figure 1C and Figure 3. Amendment and cancellation of certain claims is not to be construed as a dedication to the public of any of the subject matter of the claims as previously presented. No new matter has been added.

Claim Rejections under 35 USC §103

A. Claims 1 and 9-18 are rejected under 35 USC § 103(a) as allegedly being unpatentable over Bowen *et al.* (U.S. Patent No. 6,284,539) in view of Takeshima *et al.* (*Neuroscience* 1994 60(3):809-823).

Applicants respectfully traverse this rejection of the claims. Applicants claimed inventions result from their discovery that Nurr 1 overexpressing neural stem cells or neural progenitor cells can be induced to a dopaminergic cell fate upon co-culturing with Type 1 astrocytes of the ventral mesencephalon. Neither Bowen *et al.* nor Takeshima *et al.*, alone or together, suggest that Type I astrocytes of the ventral mesencephalon secrete a factor or factors that can induce a dopaminergic cell fate in neural stem cells or neuronal progenitor cells.

Bowen *et al.* discloses the overexpression of Nurr 1 in CNS stem cells to induce dopaminergic neurons. In Bowen *et al.*, Nurr 1 is provided as the inducing factor of dopaminergic cells as shown in Example 2 (column 11, lines 28-43) where following transfection with a plasmid encoding Nurr 1, numerous TH⁺/Nurr 1⁺ cells were found compared to sham-transfected or control-transfected cultures. This result suggests that Nurr 1 directed a portion, albeit a small portion, of neural stem cells to a dopaminergic fate. Applicants, however, have shown the induction of a

significant percentage of dopaminergic cells by co-culturing Nurr 1 overexpressing neural stem cells with Type I astrocytes of the ventral mesencephalon compared to Nurr 1 overexpressing neural stem cells without co-cultivation. For example, 70% of cells that expressed Nurr 1⁺ were induced to dopaminergic TH⁺ cells following co-culture (see page 38, lines 8-11). Bowen *et al.* does not teach or suggest that Type I astrocytes of the ventral mesencephalon secrete a factor or factors that can induce a dopaminergic cell fate in neural stem cells or neuronal progenitor cells. On the contrary, Bowen *et al.* teaches away from the use of soluble factors to induce a dopaminergic neuronal fate in neural stem cells. Applicants point to column 2, lines 33-37 of Bowen *et al.* which states "we have developed other methods to increase the number of dopaminergic cells present in CNS stem cell cultures by activating an endogenous transcriptional regulator Nurr 1, rather than by utilizing soluble proteins like Sonic Hedgehog or FGF-8." Here, Nurr 1 is used in place of soluble factors such as those provided by co-culture with Type I astrocytes to induce a dopaminergic cell fate.

Bowen *et al.* discloses co-culture of ventral mesencephalon neurons with striatal astrocytes or striatal cells but the purpose of this co-culture is directly stated to enhance the survival of post-mitotic dopaminergic neurons (column 2, lines 61-62). Clearly, this disclosure refers to cells that already have a developmental fate and clearly, the goal of the co-culture is to increase survival and not to induce of a dopaminergic neuronal fate.

Takeshima *et al.* does not cure the defects of Bowen *et al.* Takeshima *et al.* discloses that co-culture of dopaminergic neurons with ventral mesencephalon astrocytes promotes the selective survival or TH⁺ neurons versus all other neuronal cell types. As with Bowen *et al.*, the reference is referring to cells that have already committed to a dopaminergic neuron cell fate before co-culture with astrocytes of the ventral mesencephalon. Throughout the reference, the authors suggest the benefit of ventral mesencephalon astrocytes in co-culture to dopaminergic neurons is to increase survival of differentiated dopaminergic neurons. The Examiner has implied that the increase in TH⁺ cells seen in this study is the result of induction of TH⁺ cells from undifferentiated cells from the starting embryonic population. The authors, however, provide no indication that there were undifferentiated cells in the population and suggest that the increase in TH⁺ neurons in the population of neurons may be the result of selective killing of non-TH⁺ cells after DIV 14, the

induction of TH expression in non-dopaminergic neurons, or most likely that a neurotrophic factor derived from type-1 astrocytes is the cause in the increase survival of TH⁺ neurons (pages 818-819). Nowhere in the reference is there a disclosure or suggestion that Type I astrocytes of the ventral mesencephalon secret a factor or factors that can induce a dopaminergic cell fate in neural stem cells or neuronal progenitor cells.

As such, neither Bowen *et al.* nor Takeshima *et al.*, alone or together, disclose or suggest that Type I astrocytes of the ventral mesencephalon secrete a factor or factors that can induce a dopaminergic cell fate in neural stem cells or neuronal progenitor cells that overexpress Nurr 1.

The Examiner alleges that the claims do not recite limitations for the purpose of the astrocyte co-culture or factors that would be secreted by the astrocytes, or recites limitations regarding a role, instructional or otherwise, for the secreted astrocytes factors. Applicants respectfully submit that claim 1, as previously presented and currently amended for clarity, clearly provides an instructional role for Type I astrocyte factors to induce a dopaminergic neuronal fate in a neural stem cell or a neuronal progenitor cell that overexpresses Nurr 1. Claim 1 is directed toward a method of inducing a dopaminergic fate in a neural stem cell or neural progenitor cell that overexpresses Nurr 1 comprised of incubating the cells with Type I astrocytes of the ventral mesencephalon and thereby contacting the cells with one or more astrocyte factors whereby the cells that overexpress Nurr 1 are induced to a dopaminergic neuronal fate.

In view of the above, Applicants submit that the claimed invention is non-obvious in view of the references cited by the Examiner and request withdrawal of this § 103 (a) rejection of claims.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 441472001200. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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